THE THERAPY OF LIVER DISEASES*

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IF WE CONSIDER the many clinical syndromes which may be accompanied by various degrees of depression of hepatic function, it is apparent that the afflictions of the liver are almost as numerous and diverse as its multiple functions. In addition to a variety of diseases which affect primarily the hepatic parenchyma or associated biliary channels, there is a large group of metabolic, endocrine, and infectious diseases in which the major symptoms are referable to other organs, but which are often accompanied by marked alteration in hepatic function. Fortunately, the regenerative capacity of the liver is sufficiently great that few of the processes which produce alteration of hepatic function result in irreversible pathologic changes in the liver. A mere recitation and superficial description of the diseases which have been shown by clinical chemical methods to affect the liver adversely would require more time than has been made available for this presentation. The discussion will, therefore, be limited principally to a consideration of the most important organic non-surgical and non-malignant diseases of the liver, with particular attention given to current theories of basic therapy which may be employed in the treatment of these disorders. Some attention will be given at the same time to those aspects of the physiology and pathology of the liver which provide the rationale for current types of therapy. It should be emphasized at the outset, however, that in view of the extraordinary speed with which new information concerning the metabolic events occurring in the liver is being supplied from laboratories devoted to basic physiological research on this organ, any plan of therapy presented at this time must be modified and kept constantly in line with these advances.

A discussion of the problems posed by the therapy of non-obstructive, non-malignant diseases of the liver may be preceded by a statement concerning the general problems presented by those diseases which are

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characterized pathologically by destruction of the hepatic parenchyma. Actually, until we are better informed concerning the nature of the various etiological factors at work in liver disease, we accomplish most in therapy by devoting our attention chiefly toward those measures which hasten repair of the damaged liver, regardless of the nature of the agent or process initiating the disorder. In obstructive lesions of the biliary channels or in affections of the gall bladder, attention is naturally focussed on the nature of the inciting agent, often with an eye towards its surgical removal. Here, too, owing to the fact that the parenchyma of the liver rarely escapes some degree of associated damage, the alert surgeon has come to pay increasing attention to the problem of hepatic reserve, and to those factors which accelerate regeneration of liver tissue.

The last decade has been particularly fruitful in providing information on the multiple factors which make for the maintenance of optimal liver function and on the agents which stimulate growth and repair of the liver parenchyma following experimental damage to the liver. A rational plan of therapy for the liver diseases will, therefore, fall short of the ideal in so far as it neglects to take into full account pertinent information in the fields of nutrition, physiology, and biochemistry, which has been made available within the last few years.

Since chronic liver diseases stem from preceding acute processes in the liver, it would seem wise to preface a discussion of the treatment of chronic liver disease by a brief account of the medical management of acute hepatitis. Strictly speaking, the term "hepatitis" is applicable to all syndromes which arise as a result of damage to the tissues of the liver, whether the provoking agent be chemical, physical, bacterial or viral in nature. According to some workers, the term hepatitis should also cover not only the degenerative changes which occur in the organ as a result of the action of these agents, but the reactive and reparative phenomena as well.[1] As subdivisions under this classification, one may place the various forms of hepatitis, such as acute, sub-acute, chronic and suppurative. A classification has been devised by Bloomfield[2] which depicts the various subdivisions in this scheme in a most graphic manner (see accompanying diagram). The classification proposed by Bloomfield is particularly useful in enabling the clinician to keep in mind the underlying sequence of phenomena in hepatitis, and to aid him in avoiding confusion from the older terminology. In Bloomfield's

scheme the variations which may occur in the course of hepatitis are represented by: (1) Acute hepatitis progressing rapidly to death. In older terminology this would be referred to as acute yellow atrophy. (2) Acute hepatitis with apparent recovery, but with actual transition to a latent stage, with or without remissions. If clinical recovery does not follow, this may develop into a fibrotic stage, which is commonly referred to as cirrhosis. The third, and remaining group is composed of those cases in which hepatitis is latent from the start, and is masked clinically until incipient liver insufficiency supervenes. The analogy of this classification to that which has been devised for diseases of the kidney is immediately apparent. It may be recalled in this connection that until a coherent and simple classification had been devised for affections of the kidney, rational plans for the management of kidney disorders were largely defeated by a chaos of speculation regarding the nature and site of the pathological lesions. In the development of effective therapy for cardiac diseases, cardiologists have learned long ago to keep an attentive eye on the physiological status of the myocardium, and to disregard for the immediate purposes of treatment the primary etiologic factors in these diseases. The liver, like other glandular organs, has only a limited number of ways to respond to a large number of injurious agents and phenomena, and there is no valid reason to assume that the resulting pathology, except in a few reasonably clear-cut instances of liver disease, such as yellow fever, chronic passive congestion, etc., bears any distinctive etiologic label. There is even less evidence that the resulting type of metabolic disturbance bears any relation to the initial inciting process. Therapy, therefore, in non-surgical lesions of the liver should be concerned mainly with hepatitis, and the type of therapy dictated largely by a consideration of the *stage* of the hepatitis, i.e., whether it be acute, sub-acute, or chronic in its clinical manifestations.

The primary factors of importance in the therapy of hepatitis in its acute stages can perhaps best be illustrated by a consideration of the disease, infectious hepatitis. There have been few wars during the past century in which infectious hepatitis, or epidemic jaundice, as it is commonly called, has not been responsible for a significant portion of the total illness of troops not arising directly from injuries sustained as a consequence of participation in combat.[3, 4] During the present war, epidemic hepatitis has assumed even greater importance, and although the

exact number of cases among all the combatant forces of the world has not yet been revealed, there is sufficient evidence from published reports already available to lead us to believe that it is one of the more important non-combatant causes of morbidity among troops of all branches of the military service.[5]

Epidemic jaundice, however, is by no means limited to members of the fighting forces. It has been a common disease in sporadic and endemic form among young adults in civilian communities for many decades. Boarding schools, educational institutions, orphanages, and other eleemosynary institutions, have been particularly favored as sites for outbreaks of infectious hepatitis, as numerous reports from this country and England testify.[6, 7, 8] During the winter of 1921-22, the State of New York was visited over a very wide area by so-called infectious jaundice, with one report alone recording over 700 cases.[9]

The infective nature of epidemic jaundice has been clearly recognized for many years. Unquestionably the largest experiment of its kind attesting to the transmissible nature of infectious hepatitis grew quite accidentally out of an extensive program of immunization of members of the armed forces of the United States against yellow fever, with a vaccine made from chick embryo, to which a quantity of pooled human sera had been added.[10] Several recent communications deal with transmission of a disease indistinguishable clinically and pathologically from infectious hepatitis following transfusions of blood and plasma,[11] and following the use of human plasma in an epidemic of mumps.[12]

The once familiar syndrome of "catarrhal jaundice" is now regarded as identical with acute infectious hepatitis. Much of the confusion regarding this disease entity grew out of an uncritical acceptance of the original concept of acute infectious jaundice advanced by Bamberger in 1855, and strongly championed by Virchow in the decade thereafter.[5] This theory held that the initial lesion in catarrhal jaundice was a duodenitis, in some instances characterized by a mucus plug at the ampulla of Vater, followed by a spread of "catarrh" to the bile ducts with the subsequent obstruction of the biliary radicles. That the disease is one involving chiefly the parenchyma of the liver there is no longer any doubt.[13] It would appear that failure on the part of older pathologists to find primary involvement of hepatic cells in this disease was due mainly to their having been denied an opportunity to examine the liver during the acute stages.

Qualitatively the clinical features of the average case of infectious hepatitis are remarkably constant. There are, however, marked differences in the degree of severity of symptoms, ranging all the way from slight indisposition and malaise in some patients to a state of marked prostration in the exceptional case, not unlike that seen in acute yellow atrophy. In the majority of cases, a prodromal period lasting from 1 to 9 days precedes the appearance of jaundice. Occasionally it is longer, and in rare cases the prodromal period may occupy a period of 20-25 days. About 10 per cent of cases give jaundice as the presenting symptom with no other preceding clinical signs. In most cases, however, there is a well-defined prodromal stage characterized by lassitude and fatigue, nausea and almost complete anorexia. Frequently there are complaints of epigastric pain, but only rarely of pain in the upper right quadrant. Liver enlargement is present at some stage of the disease in nearly all cases showing moderate to severe icterus. The appearance of bile in the urine is observed by the patient in nearly every instance within a period of one to three days before the appearance of jaundice in the sclerae. Less frequently the patient will also have noted light or clay-colored stools during this period. Frank recrudescence of the disease, a state recognized by deterioration of the patient's condition during recovery, and leading to a return of clinical symptoms, may occur in the exceptional case.

A study of the metabolism and liver function in infectious hepatitis reveals extraordinary aberrations in almost all biochemical and physiological systems for which there are adequate tests. Except in the infrequent case presenting signs of chronic liver disease, all abnormal values for the various constituents of the blood and urine in patients with infectious hepatitis return to a normal range within 30 to 40 days. Numerous tests, covering a wide and diverse range of liver functions, have been applied to a study of this disease by many investigators. A consideration of the results obtained by various workers reveals a surprising correlation in the degrees of alteration shown by the various tests at any time during the course of the disease in any given case. In a consideration of the average case, it is hard to escape the conviction that the principal damage to the liver consequent to this disease occurs early, and that during the major part of the patient's illness we are observing only a sequence of phenomena having to do with regeneration of the liver parenchyma.

Therapy of Infectious Hepatitis

Except in the occasional case, when the disease becomes chronic, or in the rare case which terminates fatally, infectious hepatitis is a self-limited disease. Spontaneous recovery, in so far as it can be detected by clinical or laboratory means, occurs in the majority of cases within 30 to 40 days after the onset of initial symptoms. Until more specific information is at hand concerning the infectious nature of this disease, we are forced to limit our attempts at therapy to those measures which are believed to hasten repair of the damaged liver. Lack of specific information concerning a rational therapy for infectious hepatitis, however, has not prevented the development of very fixed notions regarding therapeutic regimes; and the literature, including textbooks devoted to treatment, abound with specific guides often diametrically opposed in substance and character for the management of the acutely damaged liver. According to some schools of thought, all forms of fat are to be avoided. At the same time, a diet high in protein is strongly recommended. The dietitian who is able to plan a diet high in biologically active protein without at the same time including a liberal quantity of fat deserves more commendation for her ingenuity than for her consideration of the patient's appetite. Until adequate experimental evidence can be adduced showing that diets which contain a moderate amount of fat are injurious to patients with acute non-obstructive disease of the liver, it seems unwise to prescribe diets which provide as little as 25 grams of fat daily. Anorexia is often a troublesome factor in the management of the patient in the acute stages of infectious hepatitis. Diets which are largely free of fat contribute further to the anorexia, since they are particularly unappetizing. They are also low in calories and in fat-soluble vitamins in relation to their bulk. The dictum against the inclusion of fats in the diets of patients with infectious jaundice doubtless arose from a mistaken concept of the pathology in this disease. While obstruction of the finer biliary radicles may occur, the disease is one which affects primarily the hepatic parenchyma and not the major bile passages, as claimed by Virchow. Evidence that a diet high in fat may not be desirable in the management of the damaged liver is based on results with experimental animals in which it is claimed that liver regeneration and survival of the animals is hindered by the inclusion of large quantities of fat in the diet.[14, 15] There is no good evidence, how-

ever, that inclusion of moderate amounts of fat is harmful if an adequate intake of protein and carbohydrate are provided at the same time.

That a diet high in protein is optimum for hastening repair of the liver is not universally admitted. There are reports, notably those of Mann and collaborators[16] in which it is claimed that in the dog, liver regeneration is delayed by the administration of a diet high in protein. Recent experiments of Whipple and collaborators,[17] however, in experiments on the regeneration of the liver after damage from chloroform, appear to have laid the ghost of diets low in protein, in the treatment of liver disease. All workers seem to agree on the value of a diet high in carbohydrate. Not only are diets high in carbohydrate indicated on the basis of the protective value of such diets against liver intoxication, but on a physiological basis as well. Widespread damage to the parenchyma of the liver may be accompanied by hypoglycemia, owing to low glycogen reserve. In these cases a high intake in carbohydrate may be necessary in order to maintain an adequate level of circulating glucose.

Much has been written lately concerning the use of the sulfur amino acids, notably methionine, in the treatment of liver damage due to widely different causes. The mode of action of methionine, as well as of other sulfur containing amino acids in providing protection against damage of the liver is not clear, although various hypotheses have been offered. These hypotheses vary all the way from the idea that the amino acids provide a source of readily available sulfur for direct combination with the noxious agent, to an indirect effect achieved through the lipotropic activity of the amino acid. In one laboratory it has been claimed that the protective effect of a diet high in protein against damage to the liver by chloroform can be attributed largely, if not wholly, to the methionine contained in the protein making up the diet.[18] Several reports on the use of methionine in the treatment of infectious hepatitis have recently appeared.[19, 20] The results of these experiments may be summarized by saying that in no instance were the results conclusive. A final statement on the worth of methionine in the treatment of acute hepatitis must wait, therefore, the appearance of further reports on the use of this type of therapy.

Patients presenting symptoms of severe infectious hepatitis may pose special problems with respect to the maintenance of nutrition. The patient may show a complete disinclination to eat for a period of several days. Anorexia, combined with an extraordinary tendency to lose weight

in the disease, may make the maintenance of a positive nitrogen balance difficult. Although the plasma protein concentration may show only slight alteration, there is good reason to assume that in the absence of an adequate protein intake a significant depletion in the stores of tissue protein may develop. In some cases a fall in serum albumin may be masked by an accompanying rise in serum globulin, so that the total serum protein concentration may appear unchanged. Moreover, a decrease in plasma protein is often accompanied by hemo-concentration, so that hypoproteinemia may not be perceptible unless determinations of the plasma volume are made at the same time. In order to provide adequate protein nutrition in the exceptional patient with infectious hepatitis who is unwilling to eat, the parenteral administration of a mixture of amino acids, such as that in a reinforced casein hydrolysate, may offer a practical solution to this difficulty. Several brands of casein hydrolysate are available at present for this purpose by means of which the entire protein requirement of a patient can be met for many days if the clinical state of the patient makes such parenteral administration imperative. Amino acid therapy to be of maximum effectiveness, must be supplemented with sufficient carbohydrate and fat to meet the caloric needs of the patient. Carbohydrate and amino acids may be given intravenously as a mixture. Unfortunately, the use of fat parenterally has not yet been achieved practically, so that only the oral route is available at present for its administration. Parenteral supplements of vitamins are available if desired. Except in the occasional case, however, when anorexia may provide a special need for vitamin supplements, a diet high in protein and carbohydrate with moderate fat meets readily the daily requirements of minerals and vitamins.

Bed rest, or at least limited activity, appears to be of paramount importance in the treatment of patients with infectious hepatitis. Retarded convalescence, or even recrudescence of the disease may occur following undue physical strain or exercise. Marked physical exertion, exposure to inclement weather, and convalescence from other diseases have long been associated with an increased susceptibility to infectious jaundice.[21] In this connection it may be recalled that in experimental transmission of infectious hepatitis to volunteers by means of filtrates of plasma from patients with the disease, physical strain incident to marching and manoeuvering was required in some cases to precipitate an attack.

The per cent of patients with infectious hepatitis who may be expected to develop signs of chronic liver disease is not known with certainty at the present time. In most groups the reported incidence has been low. However, objective criteria for residual damage were not met in many cases, or patients followed for long enough periods of time to have warranted the judgment that they had fully recovered. Establishment of adequate criteria to answer the question of whether or not residual damage to the liver has occurred following an attack of infectious jaundice is one of the many important problems which will tax the ingenuity of the post-war worker in the field of liver disease. Certainly a small number of patients may be expected to develop signs of chronic liver disease following an unusually severe or prolonged attack of acute infectious hepatitis. The syndrome seen in these cases is one characterized by mild jaundice and fixation of various hepatic functions at aberrant levels. The patient may recover in time or the disease may progress slowly and insidiously into a syndrome not unlike that of hypertrophic biliary cirrhosis, with or without ascites. In the treatment of these exceptional cases, those measures which have been found useful in the management of cirrhosis of the liver should be instituted.

Chronic Disease of the Liver

A syndrome consisting of a hard, stony liver with ascites, was known to Erasistratus, of Alexandria, nearly three hundred years before Christ. The disease was described later by Morgagni, Baillie and others in communications which have subsequently become medical classics. The term "cirrhosis" was applied to the syndrome by Laennec because the nodules projecting on the outer surface of the liver were "fawn or yellowish russet" in color. Many forms and varieties of cirrhosis have been described, but from the standpoint of supplying a basis for therapy there is little to be gained in a recital of the essential pathological characteristics of the lesions of cirrhosis. All forms, however, may be said to have in common three attributes, namely: (1) proliferation of connective tissue, (2) degeneration and death of hepatic cells, and (3) areas of regeneration of hepatic parenchyma.[22] There is eventually, in all long-standing affections, proliferation of connective tissue in the portal spaces with growth and extension of fibrous connective tissue into the whole hepatic lobule. The final stages of cirrhosis are accompanied by fusion of the peri-lobular connective tissue around the hepatic lobules with

subsequent deformation of the whole architectural pattern of the liver.

The pathogenesis of classical cirrhosis is obscure, and must remain so until more information is at hand concerning the development of the disease in its early stages and, perhaps, until it is possible to produce in animals a disease that is indistinguishable clinically and pathologically from cirrhosis in human subjects. It is an over-simplification of the facts to suppose that this has been done, although recent attempts with experimental dietary deficiencies have yielded results that permit us to hope that it may eventually be accomplished. Most students of the pathogenesis of classical cirrhosis agree that it is essentially a chronic diffuse inflammatory process which is initiated by an obscure type of injury, followed by proliferation of connective tissue in and about former sites of degeneration and necrosis.

For many years it has been the custom to regard fatty cirrhosis as a form of Laennec's cirrhosis. Indeed, Connor[23] has expressed the opinion that Laennec's cirrhosis is the ultimate outcome of a process of fatty infiltration. He has, moreover, described the various stages in which the syndrome described by Laennec is reached as (1) an acute fatty liver, attributable to alcohol in the main, changing slowly to a stage (2) of early but definite fibrosis, and finally (3) progressing to a classic nodular cirrhosis with reduction in size of the organ.[24] Recent experimental observations concerning the production of fatty infiltration of the liver with diets deficient in methionine and choline, and with rapid amelioration of the condition when the deficient agent is again supplied, make it appear that certain types of fatty cirrhosis belong in a separate category.

Therapy in Cirrhosis of the Liver

Chronic liver disease, with insufficiency, has posed and continues to present, one of the most complex problems of therapy which the physician encounters. Innumerable therapeutic measures have been devised within the past century in an attempt to cope with the problem of hepatic insufficiency, and with little success. Old remedies included potassium iodide, calomel, and a variety of saline purges such as vichy water and magnesium sulfate. Bile salts and other measures calculated to stimulate secretion of bile were employed with indifferent success. For a time it appeared that much might be accomplished through the use of diuretics such as acid forming salts and organic mercurials. Both

surgery and medicine provided new techniques for the treatment of cirrhosis. On the assumption that toxic agents were carried to the liver by the blood, various operations were devised by which attempts were made to shunt the blood carried by the portal vein into the general circulation. The operation of Talma, in which collateral circulation was achieved by suturing the peritoneal surface of the liver to the parietal peritoneum, had, and continues to have its advocates among members of the medical profession. Diverse as were these procedures, they had one thing in common, in that they were devised to relieve the chief complication of cirrhosis of the liver, ascites. The disease was regarded as fatal from the outset, and no hope was expressed that anything could be achieved other than securing greater comfort for the patient, and perhaps postponing exitus for a short time. From the time of the ancient physicians, medical writers have given cirrhosis of the liver a universally fatal prognosis, and nothing that has been achieved subsequently in the modern management of these patients has done much to alter this fatalistic concept.

Alcohol has always held a prominent place in the list of etiological factors proposed for cirrhosis of the liver, and as such has been particularly eschewed by the physician in planning a therapeutic regimen for his patients. The role of alcohol in the production of cirrhosis of the liver is still anything but clear. It would seem, however, that if alcohol is an important etiological factor in the production of the disease, that it is not due to its inherent toxicity for the liver, but rather to the factor of an associated disturbance in nutrition which is often an integral part of the syndrome of chronic alcoholism.

Attention was first directed to the role of faulty nutrition in the production of human cirrhosis of the liver by the studies of Rao, who in 1933 showed that a high incidence of this disease occurred among members of the population of Southern India, where alcoholism is all but unknown.[25, 26] In these areas nutritional deficiencies in protein, fat and vitamins, especially in vitamins A, C, and D, have occurred among members of the population for many years. In 1934, surveys made in Syria, where the incidence of cirrhosis is as high as it is in any part of the world, and where chronic alcoholism does not exist, showed that the diets of most members of the congested population were extremely low in protein. In Italy, in those regions where pellagra is endemic, the incidence of cirrhosis has always been high, as it has been in the southern

part of the United States, where pellagra has been a national problem since 1905. These facts, together with a growing awareness in this country of the relation betwen chronic alcoholism and vitamin deficiencies, have served to focus our attention on a possible nutritional basis for hepatic cirrhosis. This realization, together with a rapidly growing background in the production of experimental chronic liver disease in animals on diets low in protective substances has completely reoriented our therapeutic approach to the management of this distressing disease within the past several years.

Until the turn of the century, the diets prescribed by most physicians for patients with cirrhosis of the liver were generally low in all constituents. Carbohydrates were avoided because it was felt that excessive intestinal fermentation might arise, and prejudice the patient's clinical condition. Moreover, diets high in carbohydrate gave rise to diarrhea in many patients with chronic liver disease, thus providing another troublesome complication. Protein was avoided because it was believed that a damaged liver should not be further embarrassed by giving it protein to metabolize. Fat, too, was avoided on the basis that it would "stir up the bile" and add an additional load to the liver thereby. It is interesting in this connection to point out a rather glaring inconsistency, in that magnesium sulfate was prescribed at the same time in order to promote biliary secretion and drainage of the liver. Rationale for these various dietary restrictions were based on the knowledge of the central role of the liver in the breakdown of the constituents of food, and the belief that the liver should be "splinted" as it were, for the duration of the disease.

Around 1920 experiments were performed which showed that diets high in carbohydrate afforded a measurable degree of protection against intoxication with certain hepatoxic agents, such as chloroform, phosphorus, etc.[27] These observations ushered in the first really important change in the treatment of chronic liver disease from that which had been in vogue for many decades. The results achieved by Mann, who claimed that liver regeneration was depressed in dogs by diets high in protein, appeared for a time to call for diets low in protein, but sufficient carbohydrate was permitted to provide for a normal or even high total caloric intake.

Rationale for the administration of diets high in protein has been supplied from several fields of investigation. The importance of protein

in protecting the liver from damage was shown by Goldschmidt and his co-workers[28] in 1939 as a result of their dietary studies on rats, when it was concluded that a diet high in protein given before the production of prolonged chloroform anesthesia, reduced the incidence of hepatic cellular necrosis. Whipple and his associates[18] confirmed this work, and concluded, moreover, that the effects of a diet high in protein, in protecting the liver from chloroform damage, could be duplicated by the addition of methionine, and to a lesser extent of cystine, to a diet low in protein. Sebrell and associates[29] also demonstrated that in rats with cirrhosis of the liver produced by a diet low in choline and protein, improvement in the gross appearance of the liver, with hyperplastic regeneration of liver cells, occurred following treatment with choline and casein.

The rationale for a diet low in fat in the treatment of chronic liver disease stems from many sources, some valid, and some highly questionable. Obviously in the presence of obstructive lesions of the liver, the inclusion of a diet high in fat would be unwise, since under these conditions fats are not effectively digested. Also, it is known that certain lipotropic agents, such as choline and methionine, are effective in affording protection against certain types of experimental damage to the liver only if the diet is reasonably low in fat. There is some doubt, however, that the rational treatment of chronic diseases of the liver necessarily calls for a diet which is extremely low in fat. In the first place, it is impracticable to give a diet high in protein which at the same time contains little fat. Moreover, fats are rich sources of vitamins A, D, and E, and certain essential unsaturated fatty acids. Again, while it is stated that diets high in fat are displeasing to the average patient with liver disease, diets which are extremely low in fat are equally unpalatable and unappetizing. Finally, there is little evidence that diets with a moderate content of fat are prejudicial to patients with chronic liver disease.

Patek and his co-workers[30] were among the first to conclude that patients with alcoholic cirrhosis are benefited by supplements of the vitamins. It may be questioned, however, whether we should fasten the label of deficiency disease on the syndrome of cirrhosis of the liver. Certainly it cannot be regarded as an example of the classic types of deficiency diseases, such as beri-beri, scurvy, or pellagra. There is some reason, however, to regard cirrhosis of the liver as an *intrinsic* deficiency disease, in which faulty metabolism of certain essential components of

the diet may give rise to a syndrome which resembles deficiency diseases in some of its outward aspects, but which unlike the ordinary deficiency diseases does not respond in any striking or specific manner to one or a combination of vitamins.

The assumption that faulty metabolism of vitamins of the B-complex occurs in severe hepatic insufficiency is based thus far largely on speculation and analogy, since no convincing laboratory demonstration of this phenomenon has yet been made. Evidence that faulty metabolism of vitamin A occurs in patients with chronic disease of the liver is more convincing. Ninety-five per cent of the stores of vitamin A are in the liver, and analyses on cirrhotic livers for vitamin A levels reveal in many instances a concentration of less than 10 per cent of the normal amount. Patek and others[31] have shown that defects in dark adaptation may occur in patients with chronic liver disease of long standing. Night blindness and disturbances in dark adaptation in patients with hepatic insufficiency, however, are not greatly improved by the administration of vitamin A alone. Doses of vitamin A which are completely effective in the treatment of nyctalopia in patients with normal liver function are almost completely ineffective in relieving night blindness of patients with cirrhosis of the liver.[32] Beta-carotene, which is effective in uncomplicated nyctalopia, is also ineffective in the treatment of night blindness in patients with chronic disease of the liver. Since the liver is regarded as the only important site for the conversion of carotene to vitamin A, a part of the deficiency may arise as a result of the failure of the diseased liver to effect this conversion. Evidence of vitamin K deficiency in chronic liver disease is also excellent. This deficiency arises perhaps in part as a result of lowered absorption of vitamin K due to altered metabolism of the bile pigments, but chiefly it would seem, because of the faulty utilization of the vitamin by the liver. Only when considerable liver function remains in chronic disease of the liver is vitamin K effective in enhancing the prothrombin value. Patients with long-standing cirrhosis of the liver may develop a syndrome characterized by osteoporosis and osteomalacia. Here, too, although the clinical symptomatology is strongly reminiscent of chronic vitamin D deficiency, the syndrome is neither prevented nor cured by the administration of vitamin D.[32]

Evidence, therefore, is good that faulty metabolism of the fat soluble vitamins may occur as a result of chronic damage to the liver. One is

tempted to speculate on the possibility that interference with the metabolism of the water-soluble group of vitamins also occurs in severe hepatic insufficiency, although more evidence is needed to provide proof that this phenomenon occurs. Although the assumption continues to be made on clinical grounds, no evidence as clear cut as that for the aberrant metabolism of the fat soluble vitamins exists for faulty metabolism of the vitamins of the B group in cirrhosis of the liver. That deficiency in the case of vitamins A, D and K is essentially intrinsic, in contradistinction to the classical type of deficiency arising from lowered intake of these substances, is revealed in the failure to achieve satisfactory reversal of the syndrome by providing an ample supply of vitamins A, D or K, either by oral or parenteral route.

In connection with the idea that in chronic liver disease there is faulty metabolism or activation of the vitamins, it is tempting to regard other metabolic aberrations in chronic liver disease as being due to the failure of the liver to achieve synthesis of specific catalytic proteins, such as the enzymes, in sufficient quantities to meet the demands of normal metabolism. Fibrinogen, prothrombin and albumin are examples of three proteins which have their site of synthesis in the liver, and the synthesis of which is materially depressed in chronic hepatic insufficiency. There are probably many more examples of essential proteins of which the rate of synthesis is lowered in chronic liver disease, but we lack adequate techniques for their demonstration.

Most specific catalytic substances, organic as well as mineral, appear to require special protein vehicles for proper intermediation of their functions. It is possible, therefore, that the type of deficiency which we have labelled intrinsic, for want of a better term, may arise not as a result of lowered intake of the prosthetic catalyst, but through a depression in the rate of synthesis of the specific protein carrier needed to render the catalyst effective metabolically. The thiamino-proteins, and the proteins required as vehicles for the flavin and pyridine compounds might serve as examples, a deficiency in the synthesis of which would result conceivably in the production of symptoms not unlike those observed in thiamin, riboflavin and nicotinic acid deficiencies, respectively.

Optimism with respect to therapy of advanced cirrhosis of the liver is nearly always met with the statement that since much of the defect in cirrhosis appears to be a mechanical one brought about by fibrosis

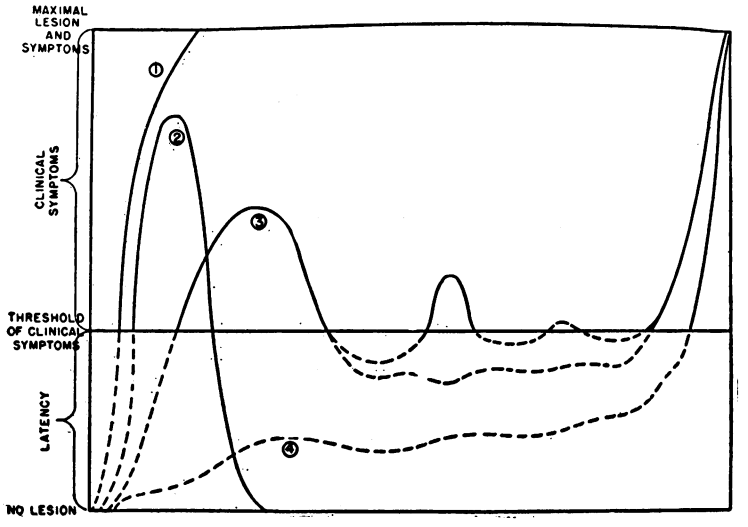
and atrophy of the liver, attempts to reverse the pathologic process are hopeless from the outset. Various explanations have been offered, for example, for the ascites which occurs in the chronic stages of disease of the liver, particularly of the Laennec type. The most common explanation for this phenomenon has been that of portal hypertension and consequent resistance to the flow of blood from the portal system through the liver. It is true that a portal hypertension may exist in many of these cases. It has been observed, however, that there are many instances when portal hypertension is marked in the absence of ascites. In other cases ascites has been recorded in the presence of a normal or only slightly elevated pressure in the portal system. Patek and Post[33] concluded that the ascites is related more directly to a deficit in plasma albumin, with consequent diminution in the colloid osmotic pressure of the blood. They have, moreover, concluded that when the concentration of albumin reaches 3.2 grams per 100 cc. of plasma, ascites disappears rapidly, although no demonstrable change has occurred in the meantime in the portal pressure. Ralli, Hoagland and collaborators[34] have shown, however, that in cases which have been treated with a regimen of combined therapy, consisting of a diet high in protein and carbohydrate and the administration intravenously of large quantities of crude liver extract, ascites may disappear and the patient show marked clinical improvement for months before any demonstrable change has occurred in the level of plasma albumin. These observations suggest that the level of albumin in the plasma is not the sole determining factor in the production of ascites. In 1940 Robinson and Farr[35] reported the presence of an antidiuretic factor in the urine of patients with nephrosis and premenstrual edema. On the premise that a similar substance might be present in the urine of patients with cirrhosis and ascites, the antidiuretic effect of aliquots of dialyzed urine from the patients was studied by Ralli *et al.* Normal urine has only slight antidiuretic activity. The urine of patients with cirrhosis of the liver and ascites was found to possess a marked antidiuretic effect when injected into hydrated rats. However, there was little or no increase of antidiuretic substance over the normal in the urine of patients with cirrhosis without ascites. Moreover, the magnitude of the effect seemed to parallel the degree of ascites.

The antidiuretic substance excreted in the urine by patients with cirrhosis of the liver and ascites has its origin presumably from the posterior pituitary, although that this is actually the case cannot be

stated at this time. That aberrant metabolism of other hormones may occur in cirrhosis of the liver is becoming increasingly certain. It is also evident that aberrant metabolism of some hormones in chronic liver disease may arise through the inability of the diseased liver to accomplish their inactivation or alteration. Certain changes associated with gynecomastia, and testicular atrophy in the male, in cirrhosis of the liver, are thought to arise as a result of the inability of the diseased liver to accomplish the inactivation of estrogen.[36, 57] Free circulating estrogen is known to be high in cirrhosis, and it may well be that certain further changes having to do with aberrant water and electrolyte metabolism in patients with chronic disease of the liver may be attributed in part to a disturbed balance between the concentration of male and female hormones arising as a result of the inability of the liver to accomplish their proper metabolism.

It would seem that many clinicians do not think that patients with active liver disease should necessarily be restricted in their physical activity. Most physicians would not dream of permitting unrestricted activity in patients suffering from impaired function of a comparable degree in other organs, such as the lungs or heart. Rest and freedom from undue physical activity is accepted as correct management in patients presenting signs of cardiac and renal insufficiency. Yet many practitioners fail to treat acute or chronic hepatitis, in which extensive damage to the liver is evident, with equal consideration. That rest or restriction of activity at once reduces the functional demands on the liver is evident from a consideration of elementary principles of physiology. Moreover, it permits careful control of the diet and medication to a degree not possible in the ambulant patient.

Aside from general measures directed toward relief of hypoproteinemia and anemia by transfusion of blood and plasma, certain specific measures directed toward relief of possible intrinsic deficiencies have been advocated from time to time. For example, marked symptomatic improvement often occurs in patients with chronic liver disease when an unrefined, water soluble extract of liver is administered parenterally. For some time we have been engaged coöperatively with Elaine P. Ralli of the Third Medical Division, Bellevue Hospital, in trying to evaluate objectively the effect of liver extract, given intravenously, as a form of replacement therapy in hepatic insufficiency.[27, 34] For this purpose a crude water soluble extract of Cohn's liver fraction G has been prepared



Variations in the course of hepatitis. *1*, Acute hepatitis progressing rapidly to death; *2*, acute hepatitis with recovery; *3*, acute hepatitis with apparent recovery but actually transition to latent stage which with or without remissions eventuates in advanced cirrhosis; *4*, hepatitis latent from the start until advanced liver insufficiency supervenes. (Bloomfield, courtesy of Am. J. Med. Sci.)

at the Rockefeller Hospital which can be given with comparative safety in large quantities by the intravenous route, provided careful tests for tolerance and sensitivity are carried out beforehand. By use of the intravenous route large amounts of liver extract can be given without the marked discomfort attendant on the continued use of potent crude extracts of liver designed for intramuscular use. While preliminary results have been encouraging, it is much too early to claim any extraordinary merit for this form of therapy. In any case, it can be used successfully only in conjunction with a full regimen of therapy which includes diet, rest, and numerous supportive measures indispensable to proper management of patients with chronic liver disease.

In the foregoing review, an effort has been made to show the influence which recent information in the field of metabolism and nutrition has had on the development of our present concept of rational treatment for hepatic insufficiency. Although we are yet far from the ultimate goal of satisfactory therapy for the hepatic diseases, some definite progress has been made, and the hope is very bright that as more

information is secured concerning the metabolic processes at work in the normal and diseased liver, increasing success in the therapy and management of these distressing disorders will be achieved.

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